ASSOCIATION OF SERUM PHOSPHORUS WITH SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC KIDNEY DISEASE. SEX MAKES A DIFFERENCE

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ABSTRACT

Background

Cardiovascular disease is the leading cause of mortality in chronic kidney disease (CKD). Serum phosphate has been associated to cardiovascular disease in the general population and this effect seems to be different according to sex. In the present study we analyze the effect of phosphate on subclinical atherosclerosis in the NEFRONA population and its effect depending on sex.

Design

Carotid ultrasound assessing the presence of plaques was performed by an itinerant team in 1687 CKD patients not in dialysis without previous cardiovascular events. Standard blood test and anthropometrical parameters were also recorded.

Results

Multivariate linear regression to model phosphate levels in patients with CKD showed an interaction of sex with age. Thus, among men, serum phosphate levels declined significantly with age almost linearly. Serum phosphate levels in women under the age of 40-45 years overlapped with those in men and then stayed above, showing and overall constant relationship. Multivariate logistic regression analysis showed that higher phosphate levels associated with a higher risk of presenting atheromatous plaque. This risk however was different according to sex. In men, phosphate levels within the normal range associated with an increased risk of subclinical atheromatosis whereas in women this risk only increased with serum levels over the normal range.

Conclusions

This study demonstrates that phosphate levels are associated with the presence of subclinical atheromatosis in a large CKD population. This effect of phosphate on subclinical atheromatosis was different according to sex, suggesting that a recommended serum phosphate levels could be different for male than for female CKD patients.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the general population [1] as well as in patients with chronic kidney disease (CKD) [2, 3]. Beyond traditional cardiovascular risk factors like hypertension, diabetes and dyslipidemia, which underestimate the risk in CKD patients [4, 5], CVD in CKD is also associated with hyperphosphatemia [6].

There is strong observational evidence showing that higher fasting serum phosphate levels are associated with a greater risk for cardiovascular disease in patients with CKD as well as in the general population [7-10]. Thus, in subjects with normal renal function, serum phosphate was positively associated with carotid intima-media thickness (cIMT) [11] and even with mortality [12] independently of traditional cardiovascular risk factors. The main mechanism involved in the pathophysiology of phosphate-induced cardiovascular risk is vascular calcification. However, high phosphate levels have been also associated with endothelial dysfunction [13, 14] which can increase the risk for atherosclerosis and hypertension [15, 16]. Thus phosphate may promote plaque development or rupture independently of its classical effects in vascular calcification [17].

The new guidelines on the assessment of cardiovascular risk [18] reiterate a key concept that has been known for decades, namely that men are at higher risk for cardiovascular disease than women independently of other known risk factors. As it has been demonstrated with traditional cardiovascular risk factors, the association of serum phosphorus with subclinical and clinical CVD in the general population could be different in men than in women [19]. For instance,

in the ARIC study, a large community-based observational study of middle aged adults predominantly without CKD, high serum phosphorus levels were associated with cIMT and CV events only in men.

On the basis of sex differences of phosphorus with subclinical and clinical CVD in the general population, we hypothesized that phosphorus levels would also be associated with greater asymptomatic atherosclerosis burden in CKD, and that this association would be different in men than in women. The results of this study show for the first time, that the effect of phosphate levels in the atherosclerosis burden of CKD patients differs according to sex.

MATERIALS AND METHODS

Patients

Study population included 1687 chronic kidney disease patients not in dialysis from the Spanish Multicenter Study NEFRONA. The Nefrona study is an observational, prospective, multicenter 4-year study aimed to assess the predictive value of non-invasive imaging techniques and biomarkers on CV events and mortality in a large cohort of Spanish patients with CKD. This is an ancillary study of the NEFRONA study, which has been extensively described [20, 21].

Briefly, patients were sequentially enrolled from 81 different hospitals throughout Spain, referred by their nephrologist between October 2010 and June 2012. The study was approved by each local ethics committee and subjects were included after providing informed consent. The tests were sequentially carried out by three trained itinerant teams composed each one of one technician and one nurse. Patients were eligible for inclusion if they had CKD (glomerular filtration rate (GFR) < 60 ml/min per 1.73 m^2) stages 3 to 5

not in dialysis and age between 18 and 74. Candidates were asymptomatic and without previous cardiovascular events at the time of recruitment.

CKD stage was based on estimated GFR in ml/min per 1.73 m^2, as determined by the four-variable Modification of Diet in Renal Disease (MDRD4) Study equation [22] and was categorized as stage 3 (GFR ≤60 ml/min and >30 ml/min per 1,73 m^2) and stage 4/5 (GFR ≤30 ml/min per 1.73 m^2 without renal replacement therapy).

Absence of cardiovascular disease was defined as absence of a history of coronary artery disease (myocardial infarction, coronary artery bypass graft surgery, coronary stent, or presence of stenosis on coronary angiography), heart failure (ejection fraction <45% or the presence of moderate or severe diastolic dysfunction by echocardiography) or peripheral arterial disease (claudication or vascular bypass surgery) or cerebrovascular disease (stroke).

Phosphate levels were categorized in ranges of clinical significance as follows: 0-3.5 mg/dl, 3.51-5 mg/dl and 5.1-10 mg/dl. Age was also categorized as follows: 18-45; 46-55; 56-65; >65 years.

Smoking background included current as well as past history. Diabetes was defined as fasting glucose level ≥ 126 mg/dl or use of hypoglycaemic medication. Blood pressure was measured before the vascular exploration 3 times in the seated position with a five minutes rest period between measurements with a validated semi-automatic oscillometer (Omron HEM-705CP). The average of the second and third readings was recorded. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥90 mmHg, or use of medications prescribed for hypertension.

Use of medications was based on clinical staff entry of prescriptions and confirmed with the patients.

Body mass index (BMI) was calculated using the following equation: weight (kg)/height (m^2). Biochemical blood test was obtained from fasting analysis in recent clinical records (within 3 months of the vascular ultrasound).

Imaging methods

All the participants in the study underwent the same carotid and femoral ultrasound protocol as previously described [23]. B-mode ultrasound imaging of the right and left carotid arteries was performed using a General Electric instrument (Vivid BT09 model) equipped with 6-13 MHz broadband linear array transducers. This examination was used to measure cIMT to identify the presence of carotid plaques according to the Mannheim consensus [24]. Thus, cIMT equal or above 1.5 mm was considered as an atheroma plaque. The far wall of the common carotid, bulb and internal carotid arteries were scanned. We measured cIMT using the semiautomated U.S. Food and Drug Administration-approved software, EchoPAC Dimension (General Electric) based on detection of the echo structures. The ultrasounds were performed by the same itinerant team and were analysed by a unique reader in a blinded fashion. Femoral ultrasound was performed with the aim to identify atheromatous plaques in the common and superficial femoral arteries.

Statistical analysis

Fisher, Spearman, Mann-Whitney and Kruskal Wallis tests were conveniently used to evaluate the effect of baseline characteristics on phosphate levels. The use of these non-parametric tests was due to the lack of normality for most variables (not shown) but also for the reduced sample size. In addition, a

multivariate linear model was fitted to assess the joint effect of the clinical variables on phosphate levels. To study the risk factors associated to the presence of plaque a colour grid was used to represent the percentage of plaques as a function of age and phosphate levels. A multivariate logistic regression model was performed to globally assess the effects of all clinical variables, including phosphate levels, on the presence/absence of plaques. A stepwise procedure based on Akaike's Information Criterion was used to determine the linear and logistic multivariate models. All the analyses were performed using R statistical package, setting the threshold for significance at 5% (α=0.05)

RESULTS

A total of 1687 CKD patients were considered for the analysis (906 stage 3, 594 stage 4 and 187 stage 5). Mean age at study entry was 59.9 ±11.8 years; 62.8% were males; 54.6% were current or former smokers; 28.5% were diabetics; 91% had hypertension; 71.1% had dyslipidaemia.

The mean serum phosphate was significantly higher in women (3.88 ± 0.72 mg/dl) than in men (3.62 mg/dl ± 0.8 mg/dl) ($p<0.00001$). 21% of the patients were on phosphate binders. Table 1 depicts the association of the serum phosphate level, using the intervals 0-3.5, 3.51-5 and 5.1-10 mg/dl, with the clinical variables, separately for men and women. Men showed a higher proportion of cases in the lowest range of phosphate while most women had phosphate levels higher than 3.5 mg/dl. Among men, those with phosphate level higher than 3.5 mg/dl were significantly younger. Mean cholesterol, LDL

and eGFR levels were significantly lower in men with a phosphate level higher than 5 mg/dl. Conversely systolic blood pressure was higher in this group of patients. The proportion of diabetics increased progressively in the three intervals considered. Among women, the proportion of smokers or former smokers was significantly lower for patients with phosphate levels between 3.51 and 5 mg/dl. Mean eGFR levels decreased progressively along the three intervals considered. Systolic blood pressure was also positively correlated with phosphate levels.

Factors associated with higher phosphate levels

The multivariate linear analysis to model serum phosphate levels (Table 2) showed a significant effect of sex, diabetes, hypertension, age, eGFR and PTH and, more interestingly, revealed that sex significantly interacted with age and also that eGFR interacted with hypertension, PTH and cholesterol. More particularly, the interaction of sex and age with respect to phosphate levels is illustrated in Figure 1, showing that as age increased phosphate levels in men decreased ($r=-0.19$, $p<0.00001$) whereas in women phosphate levels were almost unchanged with age ($r=-0.04$, $p=0.28$). In this multivariate model, total cholesterol and BMI were not significantly associated with phosphate levels and were not included.

Factors associated with the presence of atheroma plaque

Regarding subclinical atheromatosis assessed by carotid and femoral ultrasound, 69.4% of patients had atheroma plaque. Figure 2 provides a representation of the percentages of plaque by age, phosphate levels and sex,

showing that atheromatous plaque risk clearly increases with age and with phosphate levels in all the intervals considered. In addition to this, Figure 2 also shows that for phosphate levels within the normal range (3.5 to 5 mg/dl) the risk of atheromatous plaque increased at younger ages for men than for women. As expected, classical cardiovascular risk factors were more prevalent in the group of patients with plaque, who were older (63.2±8.6 vs 50.8±13.6, p=<0.0001), had a higher prevalence of diabetes (81.1 vs 18.9%, p=<0.0001) and smoking background (75.8% vs 24.2%, p=<0.0001), higher values of systolic blood pressure (146.8±21.5 vs 139.7±19.6, p=<0.0001), BMI (29.4±4.98 vs 28.05±5.29, p=<0.0001), and lower concentrations of HDL(49.6±15 vs 51.5±16, p=0.022). We did not find a graded association between a reduced eGFR and the risk for the presence of plaque. In addition, no differences were found in the presence of plaque among CKD stages (59.8% stage 3; 69.1% stage 4 and 68.8% stage 5, p=0.87).

Table 3 presents the results of the multivariate logistic regression model separately for each sex, categorizing age and phosphate levels as in the previous figure, showing that in men the classical cardiovascular risk factors (age, tobacco and diabetes) but also phosphate levels were significantly associated to plaque risk and, importantly, this effects were independent of glomerular filtration rate. Similar findings were found in women but the effect of the different ranges of phosphate was more prominent in the higher range. Further adjustment for phosphate binder use was not significant and did not modify the coefficients nor the p values. Figure 3 describe the effect of

phosphate levels on atheromatous plaque risk stratified by sex when adjusting by age, tobacco, diabetes, CRP and eGFR. A level of [3.5-5] mg/dl (within the normal range) of laboratory was associated in men to a higher risk of plaque when compared to the reference group with a phosphate level between [0-3.5] mg/dl and age between 18 and 45. However, in women a higher risk was only observed in the range between [5-10] mg/dl above the normal range of laboratory. The effect of age and phosphate levels was also significant when considered as continuous variables in the multivariate models (results not shown) for both sexes.

DISCUSSION

In our study we found that in community-living individuals with a range of kidney function from moderate to severe CKD, higher phosphate levels are significantly associated with a higher risk for atherosclerosis. This association is different according to sex, so that phosphate levels within the normal range are associated with atheromatosis only in men.

In this study we have used the presence of plaque detected by ultrasound as an indicator of atheromatosis. Prior reports have demonstrated that carotid plaque and cIMT are highly correlated, and that each of them independently predicts cardiovascular events in non-CKD cohorts [25]. Furthermore, the presence of plaque seems to have an additive role to that of cIMT in estimating cardiovascular risk in the general population [26]. Similarly, studies in patients with CKD have been unable to find a difference between coronary artery calcification, carotid plaque, and cIMT in the ability to predict self-reported prevalent CVD [27]. Thus, the presence of plaque seems to be an effective

surrogate marker for predicting cardiovascular events.

We have found that serum phosphate levels are associated with age, sex, the presence of diabetes and hypertension, the eGFR and levels of PTH and cholesterol. Interestingly, a strong interaction between sex and age was observed. Thus, as depicted in figure 1, serum phosphate levels declined with age almost linearly among men. In women under the age of 40-45 years, phosphate levels overlapped those in men and then were progressively higher. This effect remained when adjusting for variables known to affect phosphate levels as glomerular filtration rate and PTH. In this regard, it has been proven that phosphorus homeostasis is different in men and women [28]. The underlying mechanisms are uncertain, but there is evidence pointing to an effect of sex hormones in phosphate regulation [29]. Indeed, menopause and estrogen use affect serum phosphate concentrations [30].

As in the general population, traditional cardiovascular risk factors like smoking or diabetes remained associated with the presence of plaques. However phosphate levels were also related with the presence of subclinical atheromatous disease in our CKD population both, in men and women. However, serum phosphate seemed to have an effect on the presence of atheromatous plaque which was different as far as sex is considered. Thus in men, we found that fasting serum phosphate levels within the normal range were strong predictors of the presence of atheromatous plaque in CKD stages 3 to 5, as it has been described in the general population [31]. However the increased risk in women is only observed with phosphate levels over the normal range. This finding is supported by recent evidence suggesting that the association between serum phosphate levels and subclinical and clinical CVD

in the general population may be different according to sex. [32]

Whether serum phosphate is only a biomarker or a risk factor, is a question that remains to be elucidated. Thus, high FGF23 levels have been reported to be more strongly associated with vascular disease and mortality than serum phosphate levels. Furthermore, they were better predictors of adverse events in patients with normal serum phosphate [33]. In our study we did not determine FGF23 levels but, in any case, data are consistent with the hypothesis that higher phosphate levels are independent risk factors for atheromatous disease in CKD patients in which the contribution of other possible confounding factors has been ruled out. Furthermore, they provide important insights to delineate pre-clinical studies to conclusively establish whether the observed increases in atheromatosis result from a direct effect of elevations in serum phosphate or through phosphate activation of another pro-atheromatous mechanism. In turn, the identification of the pro-atheromatous mechanism induced by serum phosphate should help identify novel target for therapeutic interventions in individuals refractory to reductions in serum phosphate.

Strengths of this study include the relatively large population encompassing nearly every region of the country. Therefore, local bias was avoided. Furthermore the carotid ultrasound was performed by a unique team and analysed by one reader in a blinded fashion, avoiding the well-known interoperator bias.

However some limitations should be noted as the use of estimated GFR as opposed to direct measurement, the lack of a control group without CKD and the use of a surrogate marker instead of clinical outcome data. In addition, our study might suffer from a selection bias due to those patients who declined to

participate in the study, but this bias could not be assessed given that this information was not reported by the hospitals participating in this multicentric study. Besides, we relied on a single determination of serum phosphorus that may not accurately reflect time-averaged concentrations. In this regard, an isolated fasting morning serum phosphate measurement may underestimate 24-hour exposure. Furthermore this study lacks measurements of 1,25 hydroxyvitamin D or FGF23, which may be important mediators or confounders of the relationship between serum phosphate and the presence of atheromatous plaques [34-36]. The wide age range could also be considered a limitation of the study. However, in order to obtain an adequate sample size, the age range had to be widened. Thus, we have included pre and post-menopausal women. The perimenopausal period, at least in the general population, has been associated to higher levels of serum phosphate [37]. As menopausal status has not been recorded, we could not determine if phosphate levels were higher in menopausal women. In addition, the fact that this is an ancillary study from the NEFRONA study adds some limitations in the sense that no cause and effect relationships can be assessed and, in addition confounding variables have been selected from the available ones in the protocol.

In summary age, diabetes, smoking history and phosphate levels are variables significantly associated to atherosclerosis in CKD patients not in dialysis. Although phosphate levels within the normal range are associated to the presence of atheromatous plaque in men, this association is not found in women until they reach pathological levels. Due to this differential effect

regarding sex, recommended serum phosphate levels could be different for male than for female CKD patients

CONFLICT OF INTEREST STATEMENT

None declared

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Figure legends

Figure 1. Correlation of phosphorus with age by sex. Red and black dots represent women and men respectively. The regression line for each subpopulation is shown.

Figure 2. Observed percentages of atheromatosis plaques (carotid and femoral) by age and phosphorus in women and men. Percentages are colored in a 0 to 100% green to red scale.

Figure 3. Odds-ratios to evaluate the risk of atheromatosis depending on the phosphorus level, estimated by means of a logistic regression model adjusted by age, tobacco, diabetes, CRP and glomerular filtration rate. Reference category (OR=1) defined by those patients with phosphorus level between 0 and 3.5 mg/dl and age between 18 and 45 years, for each sex group. Segments represent 95% confidence interval for ORs

Table 1. Association of clinical variables with intervals of phosphorus, stratified by sex.

	Serum Phosphorus Level (mg/dl)			P Value
VARIABLE	**0 - 3.5**	**3.51 - 5**	**5.1 - 10**	
N of participants n/total (%)				
Men	545/1059 (51.4%)	462/1059 (43.7%)	52/1059 (4.9%)	<0.00001
Women	211/628 (33.6%)	375/628 (59.97%)	42/628 (6.7%)	
Diabetes Mellitus Yes/no (%)				
Men	135 /409 (24.8%)	165/297 (35.7%)	22/31 (41.5%)	<0.00001
Women	48/163 (22.7%)	97/278 (25.9%)	13/29 (31.0%)	0.47
Hypertension Yes/no (%)				
Men	489/55 (89.17%)	424/38 (91.40%)	51/2 (96.36%)	0.24
Women	182/29 (86.3%)	347/28 (92.5%)	42/0 (100%)	0.004
Dyslipidaemia Yes/no (%)				
Men	388/156 (71.3%)	337/125 (72.9%)	41/12 (77.4%)	0.48
Women	140/71 (66.4%)	263/112 (70.1%)	30/12 (71.4%)	0.59
Current or past smoking Yes/no (%)				
Men	396/148 (72.8%)	316/146 (68.4%)	40/13 (75.5%)	0.32
Women	68/143 (32.2%)	85/290 (22.7%)	17/25 (40.5%)	0.01
Age, years Mean (SD)				
Men	62.4±9.7	58.2± 13	56.9±11.3	<0.00001
Women	58.6±12.9	59.8±11.9	56.3±11.3	0.15
Body mass index, kg/m² Mean (SD)				
Men	29.04±3.9	28.4±4.6	28.7±5.19	0.06
Women	29.36±6.4	29.64±6.2	28.79±6.81	0.66
Total cholesterol, mg/dl Mean (SD)				
Men	179.3±35.1	177.3±39	163.2±35.1	0.01
Women	194.7 ±35	191.7±37	196.3±38.4	0.53
LDL cholesterol, mg/dl Mean (SD)				
Men	105.7±31.7	101.8±33	89.1±30.7	0.002
Women	112±32.1	108.9±33	109.6±28.1	0.56
HDL colesterol, mg/dl Mean (SD)				
Men	46.4±12.9	45.6±13.6	45.2 ±22.1	0.70
Women	57.3±14.3	56.2±15.4	57.8±17.6	0.66
Triglycerides, mg/dl Mean (SD)				
Men	146.6 ±81	156.8 ±86	159.1±81.1	0.13
Women	133.2 ±68	140.5±85	143.7±110	0.54
eGFR (MDRD) Mean (SD)				
Men	39.8±12.1	29.1±13.4	16.34±9.6	0.000
Women	36.7±12.4	28.8±12.7	15±5.8	0.000
Sistolic Blood Pressure (mmHg)				

	Serum Phosphorus Level (mg/dl)			P Value
VARIABLE	**0 - 3.5**	**3.51 - 5**	**5.1 - 10**	
Men	144.4±18.8	144.8±22	152.9±23.6	0.02
Women	140.7±20.2	145.5±23	155.9±28.7	0.000
Diastolic Blood Pressure (mmHg)				
Men	82.5±10	81.2±11.1	82.3±12	0.15
Women	81.3±10.7	81.9±10.8	85.7±12.3	0.06
Plaque presence Yes/no(%)				
Men	419/125(77)	348/114(75.3)	42/11(79.2)	0.82
Women	117/94(55.5)	230/145(61.3)	31/11(73.8)	0.03

For categorical variables the frequencies and percentages are shown. For quantitative variables the mean and the standard deviation are provided. Low density lipoprotein (LDL); High-density lipoprotein (HDL); Glomerular filtration rate estimated with the abbreviated modification of diet in renal disease equation (eGFR). Differences in categorical variables were assessed by Chi square test. Differences in continuous variables were assessed by a Mann-Whitney test.

Table 2. Multivariate linear regression to model phosphorus levels.

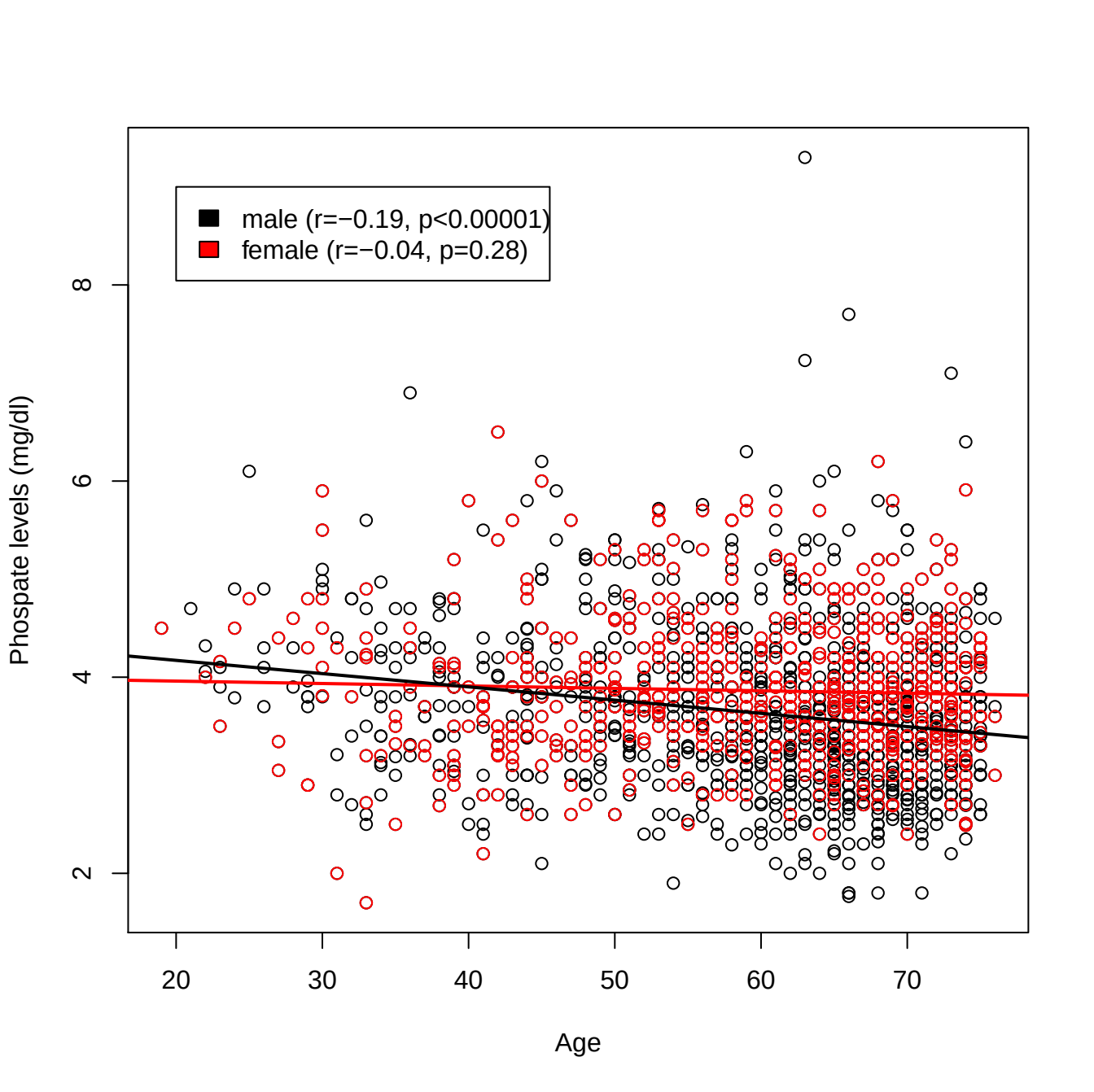
	Beta	Standard error	p-value
Constant	4.33	0.29	
Sex (Women vs Man)	-0.46	0.18	0.01
Diabetes (Yes vs No)	0.18	0.04	<0.00001
Hipertension (Yes vs No)	0.69	0.17	0.00005
Age (years)	-0.01	0.002	<0.00001
eGFR (ml/min/1.73 m^2)	-0.016	0.008	0.03
Total Cholesterol (mg/dl)	-0.0007	0.001	0.52
PTH (pg/ml)	0.001	0.0003	<0.00001
Sex:Age interaction	0.009	0.003	0.0009
eGFR:Hipertension interaction	-0.016	0.004	0.0001
eGFR:Total cholesterol interaction	0.00006	0.00003	0.049
eGFR:iPTH interaction	-0.00006	0.00001	<0.00001

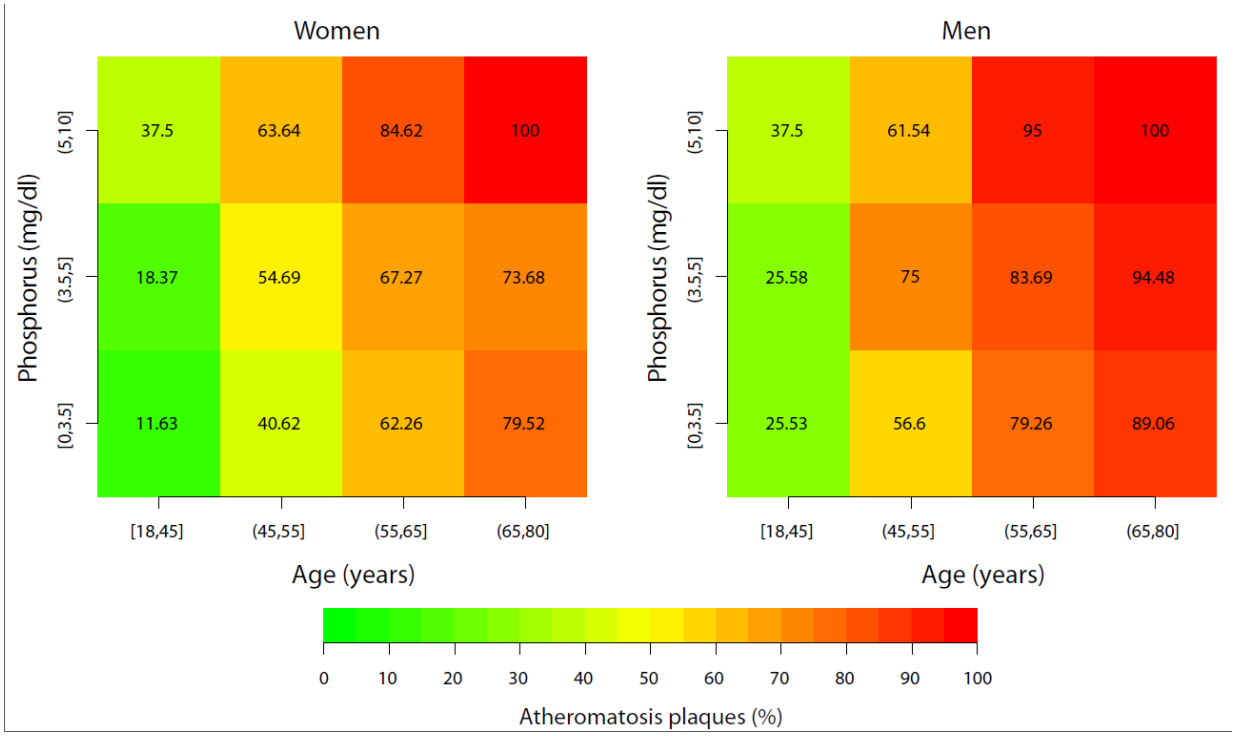
Multiple linear regression model determined with a stepwise procedure, considering all potential predictors and several interactions. Only variables with a significant effect or showing a potentially confounding influence in the model were maintained. Adjusted coefficients in the model are shown with their respective standard errors and p-values. Multiple R-squared: 0.31; Adjusted R-squared: 0.30. eGFR: estimated glomerular filtration rate. iPTH: Intact parathyroid hormone.

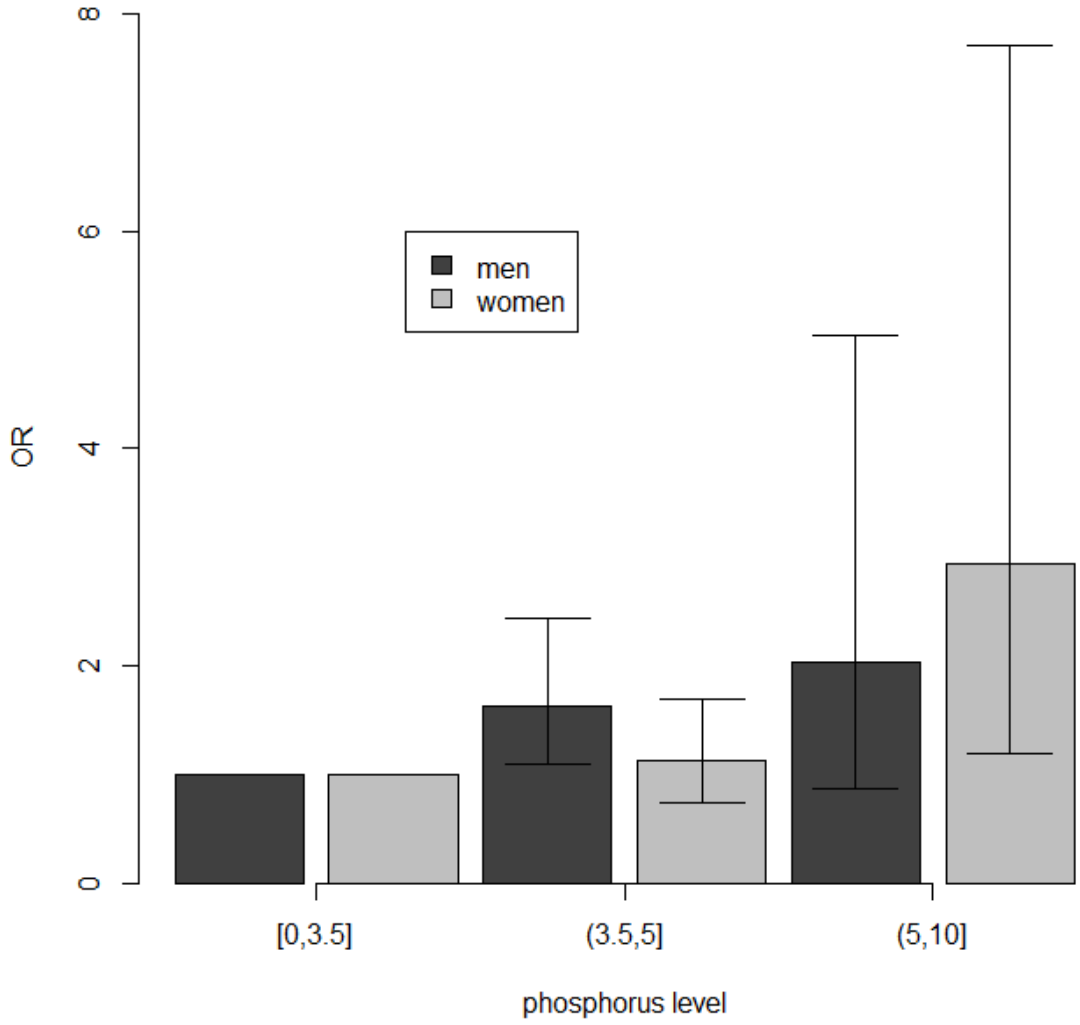
Table 3. Multivariate logistic regression to model the presence of plaque at any territory, stratified by sex.

Variable	Men				Women			
	OR	**95% CI**	**Z**	**p-value**	**OR**	**95% CI**	**Z**	**p-value**
Constant	0.09		-5.9		0.12		-5.3	
Age(45-55)	5.20	3.02-8.96	5.9	<0.00001	5.56	2.79-11.1	4.9	<0.00001
Age(55-65)	13.23	8.0-21.9	10.1	<0.00001	13.61	6.93-26.8	7.6	<0.00001
Age(65-80)	31.67	18.3-54.8	12.4	<0.00001	23.20	11.6-46.3	8.9	<0.00001
Phosphorus (3.51-5)	1.62	1.09-2.43	2.4	0.02	1.13	0.75-1.70	0.6	0.57
Phosphorus (5.1-10)	2.03	0.85-4.87	1.6	0.11	2.94	1.16-7.43	2.3	0.02
Diabetes (yes vs no)	1.89	1.24-2.88	2.9	0.003	2.08	1.32-3.27	3.2	0.001
Tobacco use (yes vs no)	2.42	1.68-3.47	4.8	<0.00001	1.92	1.21-3.07	2.8	0.006
eGFR	1.01	0.99-1.02	1.1	0.27	0.99	0.98-1.01	-0.9	0. 33
CRP	1.03	1.00-1.06	1.7	0.10	1.00	0.98-1.03	0.1	0.91

Multiple logistic regression models determined with a stepwise procedure, considering all potential predictors and several interactions. Only variables with a significant effect or showing a potentially confounding influence in the model were maintained. Odds ratio, 95% confidence interval, Z values, defined as the estimated coefficients standardized by their standard error (beta/se(beta)) and p-values are provided. Age reference interval: 18-45 years; phosphorus reference interval: 0-3.5 mg/dl; diabetes and tobacco (yes/no), eGFR and CRP as continuous variables. eGFR: estimated glomerular filtration rate. CRP: C reactive protein.


male (r=−0.19, p<0.00001)
female (r=−0.04, p=0.28)
Phospate levels (mg/dl)
2
4
6
8
20
30
40
50
60
70
Age


Women
Men
Phosphorus (mg/dl)
(5,10]
(3.5,5]
[0,3.5]
37.5
63.64
84.62
100
18.37
54.69
67.27
73.68
11.63
40.62
62.26
79.52
37.5
61.54
95
100
25.58
75
83.69
94.48
25.53
56.6
79.26
89.06
[18,45]
(45,55]
(55,65]
(65,80]
Age (years)
0
10
20
30
40
50
60
70
80
90
100
Atheromatosis plaques (%)


OR
0
2
4
6
8
men
women
[0,3.5]
(3.5,5]
(5,10]
phosphorus level